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Para-Fluorination of Anilides Using Electrochemically Generated Hypervalent Iodoarenes

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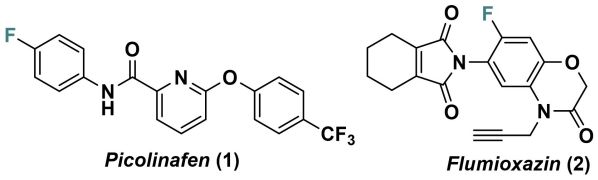
Abstract: The *para*-selective fluorination reaction of anilides using electrochemically generated hypervalent $ArIF_2$ is reported, with $Et_3N{\cdot}5HF$ serving as fluoride source and as supporting electrolyte. This electrochemical reaction is characterized by a simple set-up, easy scalability and affords a broad variety of fluorinated anilides from easily accessible anilides in good yields up to 86%.

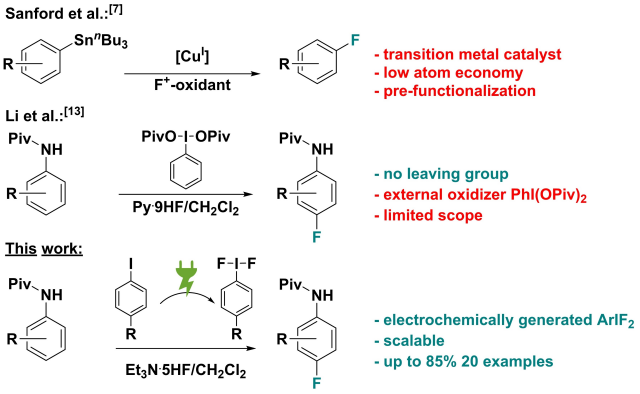
Introduction

In the field of pharmaceuticals and agro chemicals, the installation of fluoro substituents into an aryl moiety can be used to modify its metabolic stability and therefore its bioactivity.[1] Over the recent years, more fluorine containing drugs have been approved, highlighting the importance of the substance class.[2] Therefore, acquiring elegant reaction pathways to introduce fluorine, especially late stage functionalizations, are of high interest in current research.[3]

Fluoroarenes like the anilide Picolinafen (**1**) and the benzoxazinone Flumioxazin (Scheme 1) are commonly used as herbicides for wheat protection.[4] One of the first known regioselective reactions for the preparation of fluorinated arenes are the Balz–Schiemann and the halogen exchange (Halex) reaction (Scheme 2).[5] While the Halex reaction of electron deficient chloroarenes is nowadays a well-established method often used in many technical processes for the synthesis of aryl fluorides, the Balz–Schiemann reaction could not exceed preparations on lab scale, due to the challenging handling of diazonium salts. Other reagent-based pathways towards fluoroarenes use elemental fluorine or XeF_2, which are difficult to handle due to their high and not easy to control reactivity.[6] Alternative approaches employ metal-catalyzed reactions by using stannanes or boronic acids as leaving groups in combination with an "F^+"-source such as Selectfluor® or 1-fluoro-2,4,6-trimethylpyridinium triflate for the installation of fluoro substituents at the arene moiety.[7] Although these methods exhibit excellent regioselectivity and yield, they suffer from the need of complex pre-functionalization and the use of leaving moieties forming toxic waste. These aspects lower the atom economy, and the use of transition metals is questionable due to sustainability and should be avoided in pharmaceutical synthesis.[8]



Scheme 1. Selected FDA approved herbicides containing fluoroarene moieties.



Scheme 2. Conventional routes to 4-fluoro anilides in contrast to our electrochemical access.

Another sophisticated approach for the functionalization of arenes is by the means of hypervalent iodine reagents,[9] which offer unique reactivities and safe handling at ambient temperatures.[10] They are frequently used as oxidizing reagents in a broad field of synthesis, often replacing toxic transition metals.[11] In 2015, Buckingham et al. used these I(III)-reagents for the oxidative fluorination of sulfonamides, employing PIDA as oxidizing reagent in the presence of Olah's reagent (HF-pyridine).[12] However, a *tert*-butyl substituent in *para*-position as leaving moiety was crucial for a successful conversion. In

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contrast to that, Li et al. were able to conduct a *para*-selective fluorination of anilides using bis(*tert*-butylcarbonyloxy)-iodobenzene ($PhI(OPiv)_2$) in combination with HF-pyridine as fluoride source on various substrates without the use of leaving groups in good yields.[13] Nevertheless, applying more commonly used hypervalent iodine reagents as PIDA or PIFA, a significant drop in yield was observed due to the competing acetoxylation of the corresponding amide. Additionally, their method was limited to the fluorination of benzanilides.

In terms of sustainability, it is highly desirable to limit the use of external oxidants and reagent-based waste to a minimum. For these reasons, the use of electric current as renewable, traceless green oxidant for organic transformations attracted a lot of attention over the past decades. Its innovative reactivity to valuable products,[14] scalability, inherent safety and simple feasibility make this 21st century technique even more valuable.[15] In particular, the anodic functionalization of arenes has experienced attention.[16]

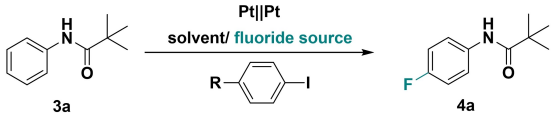
However, for a cost-efficient synthesis the work-up and the simplicity of the process has to be encountered as well.[17] The electrochemical installation of fluoro moieties is challenging and of current interest.[18] It is also possible to generate such hypervalent iodine reagents electrochemically, forming the reactive iodine(III) species in situ and use it without the need of isolation for the desired subsequent reaction.[19] In particular, the electrochemical formation of difluoroiodotoluene ($TolIF_2$) enabled a variety of fluorinations.[20] Based on our experience on electrochemical fluorination reactions, we present the fluorination of anilides, using an electrosynthetic approach.

Results and Discussion

On the basis of our previously published parameters on the electrochemical formation of difluoroiodotoluene for the synthesis of heterocycles,[21] we started our optimization studies. The screening experiments were conducted in small 5 mL undivided Teflon cells using constant current conditions and platinum sheet electrodes.[22] The conversion of pivalamide **3a** as model substrate to 4-fluoropivalamide (**4a**) served as benchmark reaction for the optimization of the electrolysis conditions. Various parameters such as the applied charge, current density, electrode material, solvent system, fluoride sources, different protecting groups, and mediators were investigated. The yield of the optimization reactions was determined by ^{19}F NMR using 4-fluorotoluene as internal standard (Table 1).

Variation of the fluoride source between $Et_3N{\cdot}3HF$, $Et_3N{\cdot}5HF$, and $Py{\cdot}9HF$ indicated that $Et_3N{\cdot}5HF$ is the most potent system (Table 1, entries 1–3). Notably, no other than the *para*-fluorinated product **4a** could be detected by ^{19}F NMR, highlighting the outstanding regioselectivity of this reaction. The necessity of the mediator could be elucidated, as an electrolysis without mediator showed only traces of **4a**. In contrast to recently published results by Lennox et al., amine·5.6HF mixtures, which proved to be beneficial for iodoaryl mediated reactions[23] gave here a lower yield (Table 1, entry 4). Next, the influence of the amount of $Et_3N{\cdot}5HF$ was observed.

Table 1. Parameter screening for the optimization of the electrochemical fluorination of pivalamide to 4-fluoropivalamide (selection).[a]



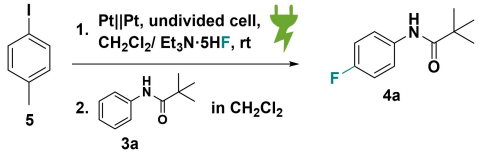
Entry	Solvent/ fluoride source, **R**=	**4a** [%][b]
1	$CH_2Cl_2 + Et_3N{\cdot}3HF$ (4:1), **R** = Me	12
2	$CH_2Cl_2 + Et_3N{\cdot}5HF$ (4:1), **R**=Me	19
3	$CH_2Cl_2 + Py{\cdot}9HF$ (4:1), **R**=Me	3
4	CH_2Cl_2 + amine·**5.6** HF[c] (4:1), **R**=Me	13
5	**CH_3CN** + $Et_3N{\cdot}5HF$ (2:3), **R**=Me	30
6	**$CHCl_3$** + $Et_3N{\cdot}5HF$ (2:3), **R**=Me	35
7	**CH_2Cl_2** + $Et_3N{\cdot}5HF$ (2:3), **R**=Me	45
8	$CH_2Cl_2 + Et_3N{\cdot}5HF$ (2:3), **R**=OMe	10
9	$CH_2Cl_2 + Et_3N{\cdot}5HF$ (2:3), **R** = ^{t}Bu	43

[a] Electrolysis conditions: Undivided cell, Pt electrodes, pivalamide (0.5 mmol), 1.5 equiv. mediator (0.75 mmol), reaction volume: 5 mL, j = 20 mA/cm^2, Q = 3.0 F, r.t. [b] Quantification by ^{19}F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard. [c] Mixture of Py·9HF and $Et_3N{\cdot}3HF$.

By using a 3:2 ratio of the ionic liquid in CH_2Cl_2 the fluorinated anilide **4a** could be obtained in 45% yield.

Since *para*-unsubstituted anilides are prone to electrochemical side reactions,[24] an ex-cell approach might be an elegant way to prevent the substrate from being electrochemically depleted. Indeed, by adding the substrate after the electrolysis of the iodoarene took place, a drastic increase in yield to 86% of **4a** could be achieved (Table 2, entry 1). Consequently, the following experiments were conducted in the same ex-cell manner. Varying the amount of 4-iodotoluene to more or less than the previous used 1.5 equivalents did not result in an enhanced yield (Table 2, entries 2–3). Additionally, carbon-based electrode materials like graphite or boron-doped diamond (BDD)[25] electrodes were investigated, but these resulted in lower yields (Table 2, entries 4–5). Therefore, platinum electrodes remained the material of choice.

Table 2. Parameter screening for the optimization of the electrochemical fluorination of pivalamide **3a** to 4-fluoropivalamide **4a** using an ex-cell approach.



Entry	Deviation from standard conditions[a]	**4a** [%][b]
1	none	**86**
2	2.0 equiv. mediator	63
3	1.0 equiv. mediator	60
4	Graphite electrodes	50
5	BDD electrodes	15

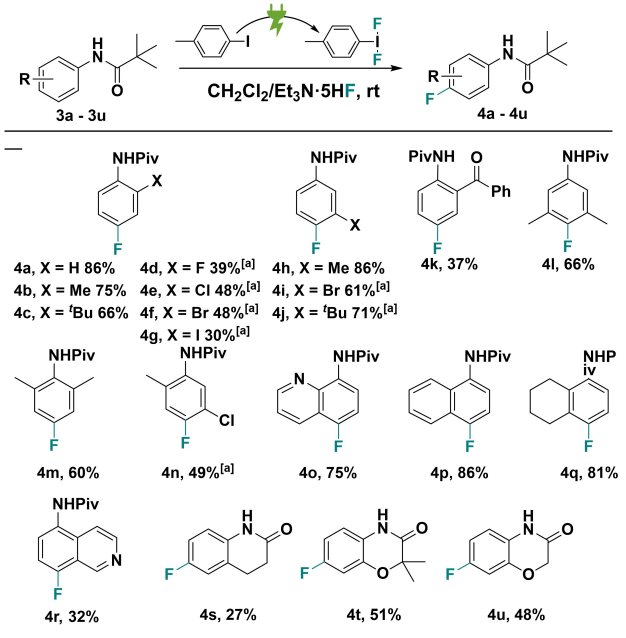
[a] Reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. mediator (0.75 mmol), Q = 3.0 F, j = 50 mA/cm^2, addition of pivalamide **3a** (0.5 mmol) after electrolysis, reaction volume: 5 mL, $CH_2Cl_2 + Et_3N{\cdot}5HF$ (2:3), r.t. [b] Quantification by ^{19}F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard.

To validate the quantification method, the TolIF$_2$-mediated fluorination under optimized conditions for the test substrate **3a** gave product **4a** in 85% isolated yield. An electrolysis of **3a** on a 2.5 mmol scale was performed with a yield of 80%, demonstrating the scalability of this conversion. Additionally, it was possible to recover up to 80% of the mediator during work-up process. With this optimized reaction protocol in hand, the scope of this reaction was explored with diverse substituents at the aryl moiety (Scheme 3). In addition to the unsubstituted anilide **3a**, several substituents in *ortho*-position were tested. The *o*-toluidine-based amide **3b** gave the corresponding fluorinated compound **4b** in 75% yield. Choosing a sterically demanding group like ^{t}butyl slightly lowered the yield of **4c** to 66%. For amides with a halo substituent (**4d**–**4g**) it was found that longer reaction times are required to improve the conversion. This clearly indicates the substituents' influence on the fluorination rate. The halogen substituted substrates gave moderate yields up to 48% (**4d**–**4g**). Surprisingly, the 2-benzoyl-substituted anilide was obtained in 37% yield. In order to investigate the effect of substituents with influence on the electron density of the arene, pivalamides bearing substituents like 2-CN, 2-OMe, 2-NO_2, 2-CO_2Me were subjected to our fluorination protocol. However, only poor yields could be observed for electron-rich amides, whereas the electron-poor amides showed no conversion of the starting materials (see Supporting Information).

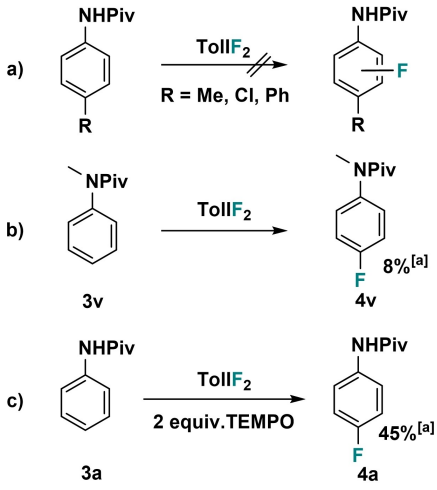
In contrast, anilides substituted in *meta*-position resulted in higher yields than their *ortho*-substituted analogues. The 3-methyl-pivalamide **4h** could be obtained in an excellent yield of 86%. For 3-bromo- and 3-^{t}butyl equipped amides **4i** and **4j** better yields were achieved as well. Furthermore, pivalamides bearing multiple substituents could be successfully converted into their corresponding fluorinated counterpart (Scheme 3, **4l**–**4j**). Even polycyclic aromatic substrates based on naphthalene and quinolone represent good substrates. The products (**4o**–**4q**) could be obtained in very good yields and no other regioisomers were detected. Only for the isoquinoline pivalamide **4r**, the conversion remained low and a moderate yield of 32% could be obtained, with the amide as lactam, the same observation could be made (Scheme 3, **4s**). Surprisingly, the fluorinated benzoxazinones **4t** and **4u**, which feature as important scaffold for herbicides, were readily formed as well.[4,26] Usually, these structures have to be formed via cyclization reactions with fluorine being introduced beforehand,[27] underlining the broad applicability of our method.

Noteworthy, the benzoxazinone substrates can be made also by an electrochemical route,[28] there is even a report of direct electrochemical fluorination of N-unsubstituted benzoxazinones under constant potential conditions using a divided cell.[29]

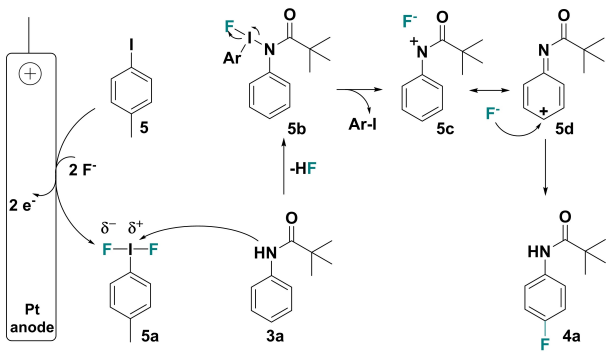
A series of control experiments were conducted to gain insights into the reaction's mechanism. Since no other than the 4-fluoro anilides were detected during optimization reactions, substrates already bearing a *para*-substituent (Scheme 4a: R=Me/Cl/Ph) were subjected to the fluorination conditions. For the 4-methyl substituted substrates, a benzylic derivatization might be envisioned as observed in previous studies.[30] However, no indication of such conversion was found here. Additionally, *N*-methylated pivalamide (**3v**) was tested for a possible fluorination as well. Here a drastic drop in yield to 8% was observed (Scheme 4b), indicating that the amide proton takes a crucial role in the fluorination process. Moreover, the occurrence of a radical reaction can be excluded, since the



Scheme 3. Synthesis of fluorinated anilide derivatives using electrochemically generated ArIF$_2$. Standard reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. 4-iodotoluene (0.75 mmol), Q=3.0 *F*, j=50 mA/cm^2, addition of amide (0.5 mmol) after electrolysis, reaction volume: 5 mL, CH_2Cl_2 + Et_3N·5HF (2:3), r.t. [a] Additional stirring time after addition of anilide: 48 h.



Scheme 4. Control experiments. Reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. 4-iodotoluene (0.75 mmol), Q=3.0 *F*, j=50 mA/cm^2, addition of amide (0.5 mmol) after electrolysis, reaction volume: 5 mL, CH_2Cl_2 + Et_3N·5HF (2:3), r.t. [a] Quantification by ^{19}F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard.



Scheme 5. Proposed mechanism for the fluorination of **3a** to **4a** mediated by anodically formed $TolIF_2$.

fluorination reaction in presence of 2.0 equivalents of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, Scheme 4c) was not completely suppressed.

From these control experiments we propose a possible mechanism as shown in Scheme 5, which is supported by other literature findings.[9b,c,31] The hypervalent iodine species **5a** is formed by electrochemical oxidation at the platinum anode and attacked by the nucleophilic nitrogen of **3a**. Hereafter, iodonium species **5b** is generated, releasing HF, followed by cleavage of the N–I bond. With this step *p*-Tol-I (**5**) is released and the positive charge of nitrenium intermediate **5c** is stabilized by the phenyl ring and can be trapped by nucleophilic attack with a fluoride ion at the *para*-position of **5d**, delivering the fluorinated anilide **4a**.

Conclusion

In summary, we established a sustainable, *para*-selective fluorination method of aromatic amides, using an electrochemically generated hypervalent iodine mediator. The electrochemical generation of $ArIF_2$ is easy to conduct with an undivided two-electrode arrangement and provides a sustainable and favorable alternative to conventional synthetic protocols. The compatibility with other substrates is given due to an ex-cell approach. Beneficially, the 4-iodotoluene could be mostly recovered during the work-up protocol. A broad scope was shown and the successful fluorination of distinct heterocycles such as quinolines and benzoxazines highlights the broad applicability of this conversion. A scale-up of this electrolysis could be conducted with a similar yield, indicating the easy scalability and robust nature of this electrochemical approach.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: anilides · electrochemistry · electrosynthesis · fluorination · hypervalent iodine

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